DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Memorandum

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From Div. of Toxicology, Additives Evaluation Branch (HFF-158) Ref 7

Subject Gum arabic and immunogenicity; updated literature survey.

To Acting Chief, Case and Advisory Branch (HFF-314)
Attention: Curtis E. Coker

Through: Dr. G. N. Biddle Kirk Biddle 3/10/88
Chief, Additives Evaluation Branch (HFF 158)

GRP 3G0287

In response to your memorandum concerning the petition (GRP 3G0287) to amend 21 CFR 184.1330 affirming gum arabic (Acacia) as GRAS for use in alcoholic beverages, a review of gum arabic literature published since the SCOGS report of 1973, using Index Medicus, the Citation Index, the SIREN data base and Med Line with a special emphasis on hypersensitivity and allergic reactions, has been performed. An earlier literature survey update was reported in a memo of May 6, 1983 (HFF-159 to HFF-335) and revealed three relevant articles. Summaries of the additional pertinent articles follow.

Category A. Anecdotal instances of human reactions.

1.) Simultaneous sensitization to gum arabic and cobalt, van Ketel, W.G., Contact Dermatitis 10, 180, 1984.

This paper describes a single case of a 44 y.o. male litho-printer that had severe eczema on the hands for 2 years duration directly attributable to gum arabic. Although patch test positive for both gum arabic and cobalt (the latter a component of the printing inks), replacement of the gum arabic only with a synthetic gum led to a cessation of symptoms.

2.) Allergic contact dermatitis due to 1,2-benzisothiazolin-3-one in gum arabic, Freeman, S., Contact Dermatitis 11, 146-149, 1984.

This paper describes a case report of a 24 y.o. male printer that had a three-month history of hand dermatitis initially attributable to gum arabic. Additional testing revealed that it was BIT, a preservative in the gum arabic, that caused the positive patch test as well as the dermatitis.

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3.) Gum arabic sensitivity associated with epidemic hysteria dermatologica, Ilchyshyn, A. and Smith, A.G., Contact Dermatitis 13, 282-283, 1985

This paper discusses a 45 y.o. female pottery-worker with a two-year history of an itchy rash of the hands who was patch test positive for gum arabic. The patient's anxieties were transmitted to her colleagues of whom a majority came to believe that they were suffering from skin trouble due to the clay (which contains 5 - 7 % gum arabic). Examination of each individual and firm reassurance regarding the uniqueness of gum arabic sensitivity achieved control of this situation.

4.) Occupational Asthma, Chan-Yeung, M. and Lam, S. American Review of Respiratory Disease 133, 686-703, 1986.

Occupational asthma has been defined as variable airway narrowing causally related to exposure in the working environment to airborne dusts, gases, vapors or fumes. Gum arabic was listed as a causative agent of occupational asthma in the printing industry. The report indicated that subjects were skin patch test positive for gum arabic, and rated a positive score in a broncho-provocation test (test details unavailable).

Category B. Immunogenicity of gum arabic in animal models.

1.) Induction of oral tolerance, in mice, to gum arabic, Strobel, S. and Ferguson, A., Food Additives and Contaminants 3, 43-46, 1986.

Inbred mice were fed either saline (control) or gum arabic (80 mg); and one week later systemically immunized by injection with the antigen (100 µg) emulsified in complete Freund's adjuvant. Mice which had been fed the antigen (gum arabic) had significant suppression of the humoral and cell mediated immune response. This demonstrates the tolerogenic ability of orally administered gum arabic. When an antigenic material in food has the capacity to induce oral tolerance, the response of the gut-associated lymphoid tissues will tend to "protect the individual against allergies, rather than sensitize", with the notable exception of "atopic" individuals, predisposed by their heredity to develop allergy to any environmental antigen.

2.) Immunogenicity, immunological cross reactivity and non-specific irritant properties of the exudate gums, arabic, karaya and tragacanth, Strobel, S., Ferguson, A. and Anderson, D.M.W., Food Additives and Contaminants 3, 47-56, 1986.

All gum preparations elicited systemic immune responses (on day 21) after immunization (200 µg gum arabic intradermally on day 0), although further processing reduced the immunogenicity. When assayed in the in vivo footpad swelling test (intradermal injection with 100 µg antigen), an indicator of specific cell mediated immunity, gum arabic was shown to be immunogenic in that intradermal challenge after immunization with gum arabic, caused a significant increase in footpad thickness (in inbred male mice).

3.) The isolation of anti-gum arabic antibodies by affinity chromatography, Pazur, J.H., Kelly-Delcourt, S.A., Miskiel, F.J., Burdett, L. and Docherty, J.J., Journal of Immunological Methods 89, 19-25, 1986.

Antibodies directed at gum arabic have been induced in rabbits intramuscularly immunized with 2 % gum arabic in Freund's adjuvant and subsequently purified by affinity chromatography. Chemical modification and inhibition experiments indicate that the 4-alpha-L-arabinofuranosyl-D-glucuronic acid units of the polysaccharide are the major immunodeterminant groups.

Category C. A review of gum arabic safety.

1.) Evidence for the safety of gum arabic (Acacia senegal (L.)Willd.) as a food additive - a brief review, Anderson, D.M.W., Food Additives and Contaminants 3, 225-230, 1986.

This review discusses the dietary, toxicological, immunological, chemical and "other" aspects of gum arabic safety. Specifically, under the section titled "Immunogenicity/allergenicity", an assessment of the clinical relevance of the allergenicity of the exudate gums (such as gum arabic), it was reported that the immune responses to the gums are "comparable, but not greater than, those elicited by common foodstuffs components, e.g. hen's ovalbumin". This conclusion is based on a 1982 paper by Strobel et al. which was cited in the May 6, 1983 memo and the 1986 Strobel paper (Category B, 1) cited above.

Discussion:

The following historical review assesses the allergenic reactions of gum arabic reported from many uses and routes of exposure.

The first group of papers describing deleterious effects attributable to acacia are for the intravenous injection of gum arabic as a blood substitute in shock and hemorrhage, during and following WWI. It was in vogue because of its supposed chemical inertness and colloidal physical properties. By 1932, 3,000 injections of acacia solution had been given to Mayo Clinic patients to combat hemorrhage and surgical shock, with only one instance of a true anaphylactic reaction occurring when a second infusion was given. In contrast, another scientist reported on the deaths of two individuals (out of an unknown number of cases) after I.V. injections of acacia. Guinea pigs were found to have anaphylactic shock symptoms upon IV injection, a possible mechanism in human reactions following IV acacia injections. A representative paper for this situation is:

Sudden death in two patients following intravenous injections of acacia, Lee, R.V.A., J.A.M.A. 79, 726, 1922.

In the 1940's and 1950's, isolated reports of sensitivity to gum arabic by inhalation were reported in the medical literature, most often occurring in the workplace. Case reports of "asthma" were usually found in industrial environments where gum arabic was a component in sprays or mists, such as the printing industry. Substitution of other compounds for the acacia alleviated the asthmatic symptoms. Two examples of such reports are:

Sensitivity to gum acacia, with a report of ten cases of asthma in printers, Bohner, C.B. et al., J. Allergy 12, 290, 1940.

Printers' asthma, Fowler, P.B.S., Lancet 1952 (2), 755, 1952.

During the same time period, a pivotal paper appeared relating allergic disorders to the ingestion of vegetable gums. Ten individuals were described as having one or more allergic symptoms upon ingestion of a gum-containing (karaya, tragacanth and/or arabic) commercial product. Instances of gastrointestinal allergies, vasomotor rhinitis and bronchial asthma were found with subsequent challenge in 1.) two subjects receiving multiple doses of 300 mg purified

powdered gum mixture (including arabic) to total doses of from 1200 to 1500 mg, 2.) two subjects receiving a 2100 mg single dose of the purified powdered gum mixture and 3.) one subject fed candies with the vegetable gums as ingredients. Only the last case was controlled and blinded by having the same individual ingest candies free of vegetable gums. The experimenter did not challenge the remaining subjects with purified powdered gum arabic singly and did not control or blind the ingestion studies. The reference is:

The vegetable gums by ingestion in the etiology of allergic disorders, Gelfand, H.H., J. Allergy 20, 311, 1949.

The 1973 SCOGS review of gum arabic noted that gum arabic has antigenic properties causing true antibody-antigen phenomena including allergenicity. The report cited the above-mentioned Gelfand paper on vegetable gums and on this basis recommended revisions of gum arabic specifications and the establishment of protein content limits. The report concluded that "There is no evidence in the available information on gum arabic that demonstrates a hazard to the public when it is used at levels that are now current and in the manner now practiced. However, it is not possible to determine without additional data, whether a significant increase in consumption would constitute a dietary hazard." The report also stressed the need for an epidemiologic survey of the population to assess the "significance of its allergenicity" and the "receptiveness to cross-allergies".

DT recommended, memo 5/6/83 (HFF-159 to HFF-335), after a review of the SCOGS report and an updated literature survey, that labels of creme-type liquors should indicate the presence of gum arabic as an additive. The survey of the gum arabic literature in the time period between the SCOGS report of 1973 and the early 1980's reported 3 papers: 1.) the isolated cases of long-term kidney transplant patients on prednisone (prescription formulated with a gum arabic binder), 2.) a 1973 paper describing rhinitis and asthma in occupationally-exposed printers, and 3.) a 1982 Strobel paper examining the immune response in mice immunized by injection with gum arabic. The only paper concerning oral administration is the first (Hypersensitivity to tablet additives in transplant recipients on prednisone, Rubinger, D. et al., Lancet 1978 (2), 689, 1978). The paper reported that 3 out of 15 transplant patients on prednisone therapy

for ten months to 5 years (unknown dose and frequency of gum arabic ingestion) had an alleviation of hypersensitivity reactions when the gum arabic was replaced with methylcellulose. The only references in this key paper go all the way back to the papers of the 1930's and 1940's; the Bohner paper cited above describing asthma in printers, a 1932 paper by Maytum, C.K. and Magath, T.B. (J.A.M.A. 99, 2251) describing reactions to patients receiving IV injections of acacia, and a 1933 paper by Spielman, A.D. and Baldwin, H.S. (J.A.M.A. 101, 444) linking bronchial asthma to occupational exposure to gum arabic in a candy factory.

The current search of the scientific literature reveals continued reports of dermal/bronchial hypersensitivity from exposure in the occupational environment. There have been no further reports on hypersensitivity reactions in humans from oral administration. Animal models have been utilized to examine the oral immunogenicity of gum arabic, such as the 1986 paper by Strobel et al. (see summarized publications, category B) which indicates the induction of tolerance when gum arabic is taken by the oral route. Finally, the review of gum arabic safety by Anderson (category C) refers to the 1982 Strobel paper (cited in the 5/6/83 memo, i.e., mice injected with gum arabic show a hypersensitivity reaction on follow-up injected challenge) and the current Strobel paper on oral tolerogenic hyporesponsiveness. Anderson concludes that "gum arabic, as defined, (is) one of the most extensively evaluated food additives. Its safety as a food additive is such that it is not considered necessary to specify upper levels of use in terms of an acceptable daily intake".

Published reports indicate that gum arabic is a human immunogenetic material, causing allergic reactions by four routes of administration, I.V. (WWI blood substitute studies), dermal (the current summaries (category A) on contact dermatitis), inhalation (occupational asthma) and oral (the Gelfand vegetable gum paper) but it is only the last which concerns its use as a direct food additive. DT has examined the number, frequency and severity of the reported instances of oral-induced hypersensitivity reactions in humans. Only two papers, the Gelfand vegetable gum paper of 1949 and the 1978 Rubinger paper on prednisone therapy patients (both reviewed in the preceding section) report effects after oral administration. Both

studies reported only a very few cases, 10 with skin reactions, five of which were challenged with a gum mixture and exhibited epigastric distress or vasomotor rhinitis in the former and 3 with allergic symptoms in the latter. Both studies had deficiencies. The paper discussing the etiology of allergic disorders following the ingestion of vegetable gums lacked controls and blinding, and failed to examine reactions with the vegetable gums singly, i.e., only tested the mixture of karaya, tragacanth and acacia. The paper examining the hypersensitivity to prednisone tablet additives provided evidence that the oral intake of tablets using acacia as a binder was responsible for the hypersensitivity reactions in three out of 15 long-term kidney transplant patients, however, there is no data on the amount of acacia consumed nor the frequency of consumption during the 10 months to 5 years they collectively were undergoing therapy.

Conclusion:

The ingestion of 1 to 2 oz. of a creme-style liquor, containing up to 20% gum arabic, at one sitting could provide a bolus dose of gum arabic at a level able to trigger a reaction in a sensitive individual. However, doses of that magnitude are regularly consumed by a large segment of the population in any one of a large number of products containing high acacia concentrations, viz. confections and frostings (12.4% permitted, 21 CFR 184.1330), hard candy and cough drops (46.5%) and soft candy (85%). The few cases presenting minor reactions, using products containing at times substantial amounts of the gum acacia, during a history of use going back more than 50 years, can be viewed as extremely weak evidence for the allergenic potential of gum arabic constituting a safety problem. Therefore, DT does not feel there is a significant body of data to support the labeling of alcoholic creme-style liquors.

Although the specific gum arabic GRAS affirmation regulation, 21 CFR 184.1330, does not require labeling, there is a requirement for the labeling of gum arabic as an ingredient under the general food labeling provisions (21 CFR 101.4). The latter allows individuals who may be allergic to gum arabic to avoid foods containing this substance because it will be listed on the product's ingredient label. Not requiring alcoholic creme-style liquors containing gum arabic to be labeled could be viewed as being inconsistent with the requirement to label foods containing gum arabic.

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James C. Griffiths 3/8/88

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